

Claims: What is claimed is:

1. An improved method of primary hormonal treatment with lesser or no toxic effect as primary treatment of early stage, low and intermediate risk prostate cancer and said primary hormonal treatment comprising of prostatic implants of steroid hormones, or its synthetic derivatives in one or more slow release formulations and permitting said drugs to be continuously released at near constant rate directly to prostate for longer periods and maintaining said formulation's serum level sufficient to effect suppression of androgen synthesis but low enough to minimize or to eliminate systemic toxicity.
2. A method according to claim 1, wherein said primary hormonal implant treatment of early stage, low and intermediate risk prostate cancer as an alternative to surgery and radiation therapy and the surgery or radiation therapy is reserved for those patients failing to said primary hormonal treatment
3. A method according to claim 1 further comprising release of said hormonal compositions to prostate for extended periods by diffusion and biodegradation from said prostatic implants in sufficient amounts to saturate the binding sites for said drug compositions in prostate and to exert their maximum tumor control activity and to follow up the biochemical tumor control by maintaining the serum PSA at a comparable low nadir value of 0.1 to 1 ng per ml as with post radiation therapy PSA values.
4. A method according to claim 1 further comprising systemic maintenance of said drug compositions for extended periods by diffusion and biodegradation from said prostatic implants at an amount effective to suppress testicular and adrenal androgen synthesis with minimum or no systemic toxicity than if said drug compositions were administered orally or by intravenous, intramuscular or subcutaneous injections at much higher doses.

5. A method of claim 1 wherein said implants comprising of hormonally effective compositions selected from the natural or synthetic derivatives from the groups consisting of estrogens, progesterones, corticosteroids, from the anti-androgen groups consisting of flutamide, bicalutamide and nilutamide.
6. A method according to claim 1 wherein said prostatic implants of said drug compositions are made as separate or in combination thereof.
7. The method of claim 1 wherein said prostatic implants are made as biodegradable fused combinations of said therapeutic drug compositions and a lipoid carrier and said fused implants containing a single or multiples of said drug formulations for their slow release direct to prostate.
8. A method according to claim 1 wherein said prostatic implants are made of Silastic capsules containing said therapeutic drug compositions as separate or in combination thereof for said formulation's slow release direct to prostate.
9. The method of claim 1 wherein said prostatic implants are made as injectable microcapsules prepared from biodegradable polymer and said microcapsules containing said therapeutic drug compositions as separate or as in combination thereof for prostatic injection as slow release implant.
10. The method of claim 9, wherein said prostatic implants are made as injectable microcapsules prepared from biodegradable polymer and said microcapsules containing said therapeutic drug compositions dispensed in sterile liquid medium in sterile syringe for direct prostatic injection as slow release implant.
11. The method of claim 9, wherein said prostatic implants are made as injectable microcapsules prepared from biodegradable polymer and said microcapsules

containing said therapeutic drug compositions dispensed in a mixture of sterile liquid mediums like normal saline, a local anesthetic and ethanol in a sterile syringe for direct prostatic injection as chelating slow release formulations when it comes in contact with tissue.

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12. A method of claim 1, wherein implanting said implant compositions comprises of retropubic implants, trans perennial implant, trans rectal ultrasound based visualization of the prostate and implantation, computed tomography based visualization of prostate and implantation or by surgically exposing and free hand implanting.

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13. The method of claim 1 wherein said prostatic implants are selected from readily available commercial pharmaceutical implant preparations of androgen suppressive steroid hormones or their derivatives and said implants containing a single or multiples of said drug formulations for their slow release direct to the prostate.

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14. An improved method of concomitant hormonal and radiation treatment of prostate cancer and said hormonal treatment comprising of prostatic implants of steroid hormones in one or more slow release formulations and permitting said drugs to be continuously released at near constant rate directly to the prostate during the radiation therapy and afterwards for longer periods and maintaining said formulation's serum level sufficient to effect suppression of androgen synthesis but low enough to minimize or to eliminate their toxicity.

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15. An improved method of concomitant hormonal and radiation treatment of prostate cancer according to claim 14, wherein said continued slow release of hormonal composition directly to the prostate during the interstitial radioactive seeds implants and afterwards for longer periods and maintaining said hormonal formulation's serum level sufficient to effect suppression of androgen synthesis but low enough to minimize or to eliminate their toxicity.

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16. An improved method of concomitant hormonal and radiation treatment of prostate cancer according to claim 14, wherein said hormonal implants to prostate is performed concomitantly with the radioactive implants to improve cure and convenience to patient than when they are implanted separately.

17. A prostatic, subcutaneous or intramuscular implant method for hormonal treatment of prostate cancer for improved tumor control and less toxicity from hormonal treatment than by administering said hormonal compositions by oral, or intravenous routes and said hormonal treatment comprising of prostatic, subcutaneous or intramuscular implants of steroid hormones and or their synthetic derivatives in one or more slow release formulations.

18. A method of claim 17, wherein said prostatic, subcutaneous or intramuscular implants methods comprising single or synergetic combination of hormonally and cytotoxically effective compositions selected from natural or synthetic derivatives from the groups consisting of estrogens, progesterones, corticosteroids and from the anti-androgen groups consisting of flutamide, bicalutamide and nilutamide and they are fused with a lipid carrier or encapsulated in Silastic capsules or formulated as injectable microcapsules as suitable slow-release prostatic, subcutaneous or intramuscular implant.

19. A method of claim 17, wherein said hormonally and cytotoxically effective compositions are continuously released at relatively constant rates to the systemic circulation by diffusion and biodegradation.

20. A method of claim 17, wherein said implants providing effective tumor control by suppression of hypothalamic LHRH and pituitary LH and FSH secretion and thereby suppression of testicular and adrenal androgen synthesis and or by their direct cytotoxic actions and said tumor control is evidenced by the decrease of serum PSA

to a low nadir value of less than 1 ng per ml and serum acid phosphatase to less than 0.8 international unit, its upper limit of normal value.

21. A method of claim 17, wherein said slow-release subcutaneous or intramuscular
5 implant for treating prostate cancer and providing minimum or no toxicity as compared to when said drug compositions were frequently administered orally or by intravenous injections at much higher doses to achieve the same rate of tumor control.
- 10 22. A method of claim 17, wherein when said implants are made as direct prostatic implants to reach said drug composition's high concentrations in the prostate and thereby to improve tumor control.
- 15 23. Slow-release anti-cancer prostate implants products for primary treatment of early stage T0- T2b prostate cancer before surgery or radiation therapy and comprising of a natural or synthetic estrogens and antiandrogens as fused with a lipoid carrier or as encapsulated in Silastic capsules or as injectable microcapsules and are suitable for prostatic implantation such that said hormonally and cytotoxically effective
20 compositions are continuously released at relatively high constant rates to the prostate and their lower concentrations reaching the systemic circulation that is effective to suppress the testicular and adrenal androgen synthesis by inhibition of LHRH, FSH and LH secretions but with lesser toxicity.
- 25 24. The said products of claim 23 being further characterized by providing effective tumor control including biochemical tumor control evidenced by the decrease of PSA to a low nadir value of less than 1 ng per ml and acid phosphatase to less than 0.8 international unit, its upper limit of normal value and having minimum or no systemic toxicity associated with said composition's prostatic implants than if they
30 were frequently administered orally or by intravenous, intramuscular or subcutaneous injections at much higher doses to achieve the same results.

25. Slow-release anti-cancer prostate implant product of claim 23, wherein said single drug formulation is made from any one of the drugs from a group consisting of DES, estradiol 17- β , iodoestradiol, progesterone, flutamide, bicalutamide, nilutamide and estramustine.

26. Slow-release anti-cancer prostate implant product of claim 23, wherein said synergetic two drugs formulations comprises of DES and prednisolone, DES and flutamide, DES and progesterone, estradiol 17- β and prednisolone, estradiol 17- β and progesterone, estradiol 17- β and flutamide, iodoestradiol and prednisolone, iodoestradiol and flutamide, iodoestradiol and progesterone, estramustine and prednisolone, estramustine and flutamide and estramustine and progesterone.

27. Slow-release anti-cancer prostate implant product of claim 23, wherein said synergetic three drugs formulations comprises of DES, prednisolone and flutamide, DES, flutamide and progesterone, estradiol 17- β , prednisolone and flutamide, estradiol 17- β , progesterone and flutamide, iodoestradiol, prednisolone and flutamide, iodoestradiol, progesterone and flutamide.

28. Anti-cancer products of claim 23, wherein said compositions comprising of single or synergetic combination of hormonally and cytotoxically effective amount of a natural or synthetic derivatives from the groups consisting of estrogens, progesterones, corticosteroids, from the anti-androgen groups consisting of flutamide, bicalutamide and nilutamide, and from the cytotoxic groups of drugs like estramustine in same or separate slow release biodegradable formulations as fused with a lipid carrier suitable for prostatic implantation.

29. Anticancer products according to claim 23, wherein said single or synergetic combination of hormonally and cytotoxically effective amounts of formulations as fused with a lipid carrier suitable for prostatic implantation such that said

compositions are continuously released at relatively constant rates for longer periods and the contents of said compositions being kept in amounts effective to suppress tumor growth and to suppress testicular and adrenal androgen synthesis with minimum or no systemic toxicity than if said drug compositions were frequently administered orally or by intravenous, intramuscular or subcutaneous injections at much higher doses to achieve the same results as by said low dose prostatic implants.

30. Anticancer products of claim 23, wherein said single or synergetic combinations of hormonally and cytotoxically effective amounts of natural or synthetic estrogens, progesterones, cortisone and their derivatives, flutamide, bicalutamide and nilutamide, and estramustine in same or separate slow release Silastic capsules suitable for prostatic implantation.

31. Anticancer products according to claim 23, wherein said single or synergetic combination of hormonally and cytotoxically effective amounts of formulations as slow release Silastic capsules suitable for prostatic implantation such that said compositions are continuously released at relatively constant rates for longer periods and the contents of said compositions being kept in amounts effective to suppress tumor growth and to suppress testicular and adrenal androgen synthesis with minimum or no systemic toxicity than if said drug compositions were frequently administered orally or by intravenous, intramuscular or subcutaneous injections at much higher doses to achieve the same results as by said low dose prostatic implants.

32. Anticancer products according to claim 23, wherein said anti-cancer products comprising of single or synergetic combination of hormonally and cytotoxically effective amounts of natural or synthetic derivatives from the groups consisting of estrogens, progesterones, corticosteroids, from the anti-androgen groups consisting of flutamide, bicalutamide and nilutamide in same or separate slow release injectable microcapsules suitable for prostatic implantation.

33. Anticancer products according to claim 32, wherein said single or synergetic combination of hormonally and cytotoxically effective amount of formulations as injectable microcapsules suitable for prostatic implantation such that said compositions are continuously released at relatively constant rates and the contents of said compositions being kept in amounts effective to suppress tumor growth and to suppress testicular and adrenal androgen synthesis with minimum or no systemic toxicity than if said drug compositions were frequently administered orally or by intravenous, intramuscular or subcutaneous injections at much higher doses to achieve the same results as by said low dose prostatic implants.

34. Anticancer products according to claim 23, wherein said implant products comprising of natural or synthetic derivatives from the groups consisting of estrogens, progesterones, corticosteroids, from the anti-androgen groups consisting of flutamide, bicalutamide and nilutamide and are made as separate or as mixtures of two or more thereof and fused with a lipid carrier.

35. Anti-cancer prostatic implant products according to claim 23, wherein said biodegradable prostatic implants comprise of natural or synthetic derivatives from the groups consisting of estrogens, progesterones, corticosteroids, from the anti-androgen groups consisting of flutamide, bicalutamide and nilutamide and are made as separate or as mixtures of two or more thereof as injectable microcapsules.

36. Anti-cancer prostatic implant products of claim 23, wherein said prostatic implants comprises of natural or synthetic derivatives from the groups consisting of estrogens, progesterones, corticosteroids, from the anti-androgen groups consisting of flutamide, bicalutamide and nilutamide and are made as separate or as mixtures of two or more thereof in Silastic capsules.

37. Anti-cancer prostatic implant products of claim 23, wherein said natural and synthetic estrogens, progesterones, cortisone and its derivative's serum level is being

kept at low but sufficient concentration to suppress testicular and adrenal androgen synthesis and to minimize and or to eliminate systemic toxicity associated with them if they were administered orally or by intravenous, intramuscular or subcutaneous injections at much higher doses to effect androgen suppressive treatment of the prostate cancer.

38. A prostatic, subcutaneous or intramuscular slow-release hormonal implant method and products comprising single or synergetic combination of hormonally and cytotoxically effective compositions selected from the natural or synthetic derivatives from the groups consisting of estrogens, progesterones, corticosteroids, from the anti-androgen groups consisting of flutamide, bicalutamide and nilutamide and they are fused with a lipoid carrier or encapsulated in Silastic capsules or formulated as injectable microcapsules as suitable slow-release prostatic, subcutaneous or intramuscular implantation and implanting said products for the treatment of early and advanced stage prostate cancers or as hormonal treatment combined with radiation.

39. A method and product of claim 38, wherein said tumor control is evidenced by tumor regression and the return of pre-treatment elevated serum PSA to a low nadir value of less than 1 ng per ml and serum acid phosphatase to less than 0.8 international unit, its upper normal limit value.

40. A method and product of claim 38, wherein said hormone implant treatment as lesser-cost androgen suppressive treatment.

41. A method and product of claim 38, wherein said slow-release hormone implant treatment as hormonal prophylaxis against developing the prostate cancer in high risk group of men by slow release of androgen suppressive steroids from said hormone implants to the prostate in higher concentrations and their serum concentrations kept as low as just sufficient to suppress the androgen synthesis with none or minimal

systemic toxicity and to follow up of any evidence of potential tumor development by periodic estimations of serum PSA and acid phosphatase which under said treatment will be at a low nadir value of less than 1 ng per ml for PSA and less than 0.8 international unit for serum acid phosphatase.

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PROSTATIC HORMONAL IMPLANTS TREATMENT OF THE PROSTATE CANCER

Abstract:

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An improved method and products for the primary hormonal treatment of early stage, low and intermediate risk prostate cancers by prostatic implants of androgen suppressive drugs formulated as fused with a lipid carrier or encapsulated in microcapsules or in Silastic capsules is provided. Such prostatic implants renders a constant slow-release of their contents to the prostate for extended periods by biodegradation and diffusion. It facilitates higher prostatic and lower systemic concentrations of androgen suppressive hormones. Because of their high prostatic and lower systemic concentrations, tumor control is much improved and the their systemic toxicity is minimized. Tumor control after such primary hormonal implant treatment is followed by clinical examinations and the biochemical tumor control is followed by periodic estimations of serum levels of PSA and acid phosphatase. More complex and expensive surgery or radiation therapy for this group of good prognostic early stage prostate cancer is reserved for those patients failing to this primary hormonal treatment. It will preserve potency more than by surgery or radiation therapy. Furthermore, it would reduce the cost of treatment for early stage prostate cancer significantly. Androgen suppressive hormonal implants to the prostate before, during or after lower dose conventional radiation therapy would also facilitate equal or better cure rates of localized prostate cancer as compared to the more complex and toxic higher dose radiation therapy.